REMARKS

The Office Action of October 17, 2002 has been received and its contents carefully considered.

Claims 5-21 have been canceled and new claims 35-43 have been added herein.

Cancelled claim 15 has been divided into new claims 35 and 36 directed to drug composition comprising -^{17}OH as a solvent, and new claims 40 and 41 directed to a drug composition comprising -^{14}NH or -^{33}SH as an active ingredient.

Specific examples that are in accordance with new claim 35 correspond to Examples 2 and 4 (agent for humor or body liquid drug (postoperative restoring liquid) using water (^{17}O) as a solvent), as disclosed in the present specification.

Further, the new independent claims 36 and 41 have the recitation "a concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the medicament". That is, the concentration of the active ingredient in the drug composition of claims 36 and 41 of the present application is equal to the concentration of the active ingredient in the medicament before dissolving it in a solvent of the present drug composition. This recitation is based on the descriptions on page 7, lines 8 to 14 and page 8, lines 15 to 18 (corresponding to page 8, lines 2 to 9 and page 9, lines 12 to 17 of the original specification) of the specification now on file. The present drug compositions of claims 36 and 41 contain a compound which comprises at least one member selected from the group consisting of the -OH group (claim 36) or the -NH and -SH groups (claim 41) in its chemical structure, and the whole or a part of the O, N or S atoms constituting the respective groups are substituted with their respective isotopes ^{17}O, ^{14}N or ^{33}S. When the O, N or S atoms in the present drug

composition is substituted with its stable isotope ^{17}O, ^{14}N or ^{33}S, then the elementary constituents, formulation, constituents of the drug composition *per se* are unchanged by said substitution with the stable isotope. Accordingly, the active ingredient and the concentration thereof in the resulting drug composition comprising ^{17}O, ^{14}N or ^{33}S as a solvent or an active ingredient are the same with that of the drug composition comprising O, N or S atoms before the substitution.

Thus, the present drug compositions can attain the object of the present invention, providing a medical drug that enables to externally detect the effective circulation or distribution thereof in a target organ or tissue in vivo where it is needed, by nuclear magnetic resonance method, before or simultaneously with the administration of a therapeutic agent to each patient; and providing a pharmacokinetic-diagnostic agent which can provide for each patient information on circulation and distribution of the drug in vivo, as is disclosed on page 5, lines 10 to 16 and lines 21 to 25 (corresponding to page 5, line 23 to page 6, line 3 and page 6, lines 8 to 12 of the original specification).

Regarding method claims 22 to 34 now on file, applicants request the Examiner to examine them with the new composition claims 35 to 43 at the moment. If the composition claims 35 to 43 are found to be allowable, applicants agree to rewrite these methods into claims dependent on the composition claims.

Claims 1-20 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The Examiner states that claims 1-20 are vague and indefinite because it is not clear what the composition comprises. The Examiner asks three questions in explaining why he considers the claims to be indefinite.

First, the Examiner asks whether the composition is a therapeutic, nutritional, infusion, or a diagnostic composition containing compounds wherein at least one member comprises ^{17}OH, ^{14}NH or ^{33}SH in its chemical structure. Second, the Examiner further asks whether the composition comprises the compounds previously mentioned and an additional therapeutic, nutritional, infusion or diagnostic agent. Third, the Examiner asks how the compounds can be a sugar, amino acid, additive or solvent when they appear to be claimed as therapeutic, nutritional, infusion or diagnostic agents.

The Examiner states that the claims were interpreted to mean a drug composition wherein a therapeutic, nutritional, infusion or diagnostic composition contains compounds wherein at least one member comprises $-^{17}OH$, $-^{14}NH$ or $-^{33}SH$.

In response, applicants point out that claims 1-14 were previously cancelled and therefore the rejection as to claims 1-14 is considered moot.

Further, as noted above, claims 15-21 have been cancelled.

Applicants submit that new claims 35 to 43 comply with the requirements of the second paragraph of 35 U.S.C. § 112.

With respect to the Examiner's comments concerning what the composition comprises, as is defined in new claims 35 to 43, applicants submit that it is clear what the composition comprises.

Regarding claims 35 to 39, the present drug composition is a mixture solution wherein an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents is dissolved in a solvent comprising at least one $-^{17}OH$ in its chemical structure. In other words, the drug composition defined in claims 35 to 39 comprises both of a solvent comprising at least one $-^{17}OH$ in its chemical structure and an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents; and in the mixture solution of the present drug composition, the active ingredient of the medicament is dissolved in the solvent comprising at least one $-^{17}OH$.

Regarding claims 40 to 43, the present drug composition is a mixture solution wherein an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, and containing a compound comprising at least one of $-^{14}NH$ or $-^{33}SH$ in its chemical structure is dissolved in a solvent. In other words, the drug composition defined in the claims 41 to 43 comprises both of a solvent and an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, and containing a compound comprising at least one of $-^{14}NH$ or $-^{33}SH$ in its chemical structure; and in the mixture solution of the present drug composition, the active ingredient of the medicament comprising $-^{14}NH$ or $-^{33}SH$ is dissolved in a solvent.

With respect to the Examiner's comments concerning the use of water as an aqueous solvent, applicants point out that the recitation that the aqueous solvent is water now appears in

claim 38, which depends from claims 35 and 36 directed to the drug composition comprising -^{17}OH as a solvent.

Accordingly, applicants submit that the claims comply with the requirements of the second paragraph of 35 U.S.C. 112 and request withdrawal of this rejection.

Claims 14-20 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Hopkins et al.

Applicants submit that Hopkins et al do not disclose or render obvious the present claims and, accordingly, request withdrawal of this rejection.

The Examiner asserts that Hopkins et al teach compositions comprising oxygen-17 compounds as potential NMR T2 contrast agents and the effects H_2-^{17}O on proton solutions and living tissues.

According to the Examiner, Hopkins et al teaches that it has incorporated oxygen-17 into a larger molecular species, such as glucose. Thus, it is the Examiner's position that Hopkins et al teach compositions comprising oxygen-17 containing glucose or oxygen containing water.

The Examiner further states that the effects of oxygen-17 on the proton bonded thereto are an inherent property of the compound.

In response, and as is defined in claim 35, the present invention is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the solvent comprises at least one -^{17}OH in its chemical structure, and ^{17}O in the -^{17}OH exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of

a living body with said H proton bonded to the ^{17}O, thereby enabling detection by nuclear magnetic resonance. That is, the essential constituents of the present drug composition of claim 35 are a solvent comprising at least one -^{17}OH in its chemical structure and an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents. For example, as is specifically disclosed in Examples 2 and 4 (agent for humor or body liquid drug (postoperative restoring liquid) using water (-^{17}O) as a solvent) of the present specification, the drug composition defined in claim 35 is a mixture solution wherein the active ingredient of the medicament ("KN replenisher 4A", postoperative restoring liquid) is dissolved in water containing ^{17}O as solvent. The drug composition is a mixture solution containing both of a solvent comprising -^{17}OH in its chemical structure and an active ingredient of the medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents.

On the other hand, Hopkins et al merely state that water containing -^{17}O may be used as contrast agents by administering it in a living body, and there is an application possibility for a -^{17}O compound (e.g. glucose that contains ^{17}O) as a use of contrast agents in MRI.

As comparing the present drug composition with the compound disclosed in Hopkins et at, the difference in the constitution between the two is quite clear. The compound disclosed in Hopkins et al the $H_2{}^{17}O$ per se or the glucose that contains ^{17}O, while the present drug composition essentially comprises both of a solvent comprising -^{17}OH and an active ingredient of the medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents. Particularly, "glucose containing ^{17}O", disclosed in Hopkins et al is the glucose comprising ^{17}O in its chemical structure, and thus, it is clearly

distinguishable from the present drug composition, e.g., the drug composition wherein glucose as an active ingredient of a medicament is dissolved in a solvent comprising ^{-17}OH. Hopkins et al are quite silent as to a composition wherein an active ingredient of the medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents is dissolved in a solvent comprising at least one ^{-17}OH in its chemical structure.

Accordingly, applicants submit that the compound disclosed in Hopkins et al is clearly distinguishable from the drug composition defined in claim 35.

In this respect, the Examiner points out on page 4, lines 1 to 2 of the Official Action, that Hopkins et al and the present invention both teach compositions comprising ^{17}O-containing glucose or ^{17}O containing water. However, as mentioned above, Hopkins et al merely disclose "$H_2{}^{17}O$" or "glucose containing "^{17}O", and Hopkins et al do not teach "compositions comprising ^{17}O-containing glucose or ^{17}O-containing water".

Thus, applicants submit that the present drug composition defined in claims 35 to 39 sufficiently has novelty over Hopkins et al, since Hopkins et al do not at all disclose a drug composition wherein an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents is dissolved in a solvent comprising at least one ^{-17}OH in its chemical structure.

Further, with respect to claims 40 to 43, Hopkins et al do not disclose or suggest a drug composition wherein the active ingredient of the medicament contains a compound comprising at least either one of ^{-14}NH or ^{-33}SH in its chemical structure. Claims 40 to 43 are patentable over Hopkins et al for this reason alone.

As has been discussed above, the present invention, as defined in claim 35 and 36, is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the solvent comprises at least one $^{-17}$OH in its chemical structure, and ^{17}O in the $^{-17}$OH exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton bonded to the ^{17}O, thereby enabling detection by nuclear magnetic resonance. That is, the essential constituents of the present drug composition defined in claims 35 to 39 are both of a solvent comprising at least one $^{-17}$OH in its chemical structure and an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents.

Applicants submit that the recitations of claims 35 and 36 make the difference between the compounds of Hopkins et al and the present composition clear.

Applicants submit further that it is clear that the constituents of the present drug composition, as defined in claims 35 and 36, are both of "a solvent comprising at least one $^{-17}$OH in its chemical structure" and "an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents". The recitation "selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents" is a positive recitation of the active ingredient of the medicament in the present drug composition.

Accordingly, applicants submit that the recitation "selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents" is not a preamble

pointed out by the Examiner, but is an essential limitation in order to define the present invention.

Applicants also submit that the present drug composition defined in claims 35 to 43 is clearly distinguishable from the glucose containing ^{17}O disclosed in Hopkins et al.

In addition, applicants further explain the effect of the present application and the unobviousness of the present invention. Applicants also enclose an executed Declaration under 37 C.F.R 1.132 which contains additional examples of the present invention.

As is disclosed on page 10, line 24 to page 11, line 7 (corresponding to page 12, lines 3 to 16 of the original specification) of the present specification, in case of electrolyte infusion, it is necessary to choose the kind and the concentration of the electrolytes contained therein being suitable for the disease state of each patient, and decide a proper drug composition for the patient. This is because the biodistribution of the drug in a living body is different depending upon the kind and the concentration of the electrolytes contained in the electrolyte infusion. That is, in such a drug composition comprising electrolytes (active ingredients) as a solute and water as a solvent, the biodistribution of water as a solvent varies depending on the combination of the solutes and solvent (water). As a result, the effect of the drug composition varies as well.

The biodistribution of the solvent (water) administered to the living body, as well as the effect of the drug composition, vary depending on the combination of the solutes and the solvent (water), i.e., depending on various constitutions of the drug composition. The present drug composition enables to detect said biodistribution by nuclear magnetic resonance. Thus, according to the present drug composition, the information on circulation and distribution of the drug in vivo can be confirmed simultaneously with the administration of a therapeutic agent to

each patient; and besides the information on circulation and distribution of the drug in vivo can be confirmed by administering the present drug composition before the administration of the objective therapeutic agent to each patient. Accordingly, the present drug composition contributes to an estimation of the effect of the medicaments and a proper selection of the medicaments.

None of the cited references discloses or suggests the present drug composition, wherein the biodistribution of the solvent and the effect of the drug in vivo vary depending upon the kind and concentration of the constituents of the drug, and said biodistribution can be detected by nuclear magnetic resonance. Accordingly, one of ordinary shell in the art could not have conceived the present drug composition on the basis of the cited references.

As is shown in the enclosed Declaration, applicants conducted additional experiments in order to support the above-mentioned arguments. In the additional examples, two kinds of drug compositions wherein the constituents are different from each other were formulated, and the biodistribution of the $^{-17}$O-containing water was determined in various organs in rat. In this respect, applicants enclose copies of a catalogue for "D-mannitol injection" (Exhibit A) and a catalogue for "KN replenisher 4A" (Exhibit B), with partial English translations. The "D-mannitol injection" and "KN replenisher 4A" employed in the additional examples are widely used and available in Japan.

In view of the above, applicants submit that claims 35 to 43 are patentable over Hopkins et al and, accordingly, request withdrawal of this rejection.

Claim 21 has been rejected under 35 U.S.C. § 103 as allegedly being unpatentable over Hopkins et al as applied above, and further in view of the newly cited patent to Pines et al.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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Respectfully submitted,

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